1.0 PURPOSE

In order to ensure that human subject clinical trials conducted at sites funded by the Division of AIDS (DAIDS) is of the highest quality and fulfills the goals of collecting complete and accurate trial data while ensuring the safety of participants, each principal investigator (PI) will be responsible for implementing an internal Quality Management (QM) Plan. The Plan should be focused on providing the site staff with the means to identify problems in protocol implementation and regulatory compliance, develop corrective actions, and document the steps taken to resolve problems.

2.0 SCOPE

This policy applies to all clinical research sites conducting DAIDS funded and/or sponsored clinical trials.

3.0 BACKGROUND

Internal Quality Management is part of a system of clinical trial oversight required for local conduct of DAIDS funded and/or sponsored studies. The development and implementation of a QM Plan that addresses key aspects of clinical research activities will help ensure that the rights and safety of participants are protected and that data collected is accurate and complete. Since extensive external monitoring at every site is not feasible, the DAIDS has promoted and instituted this requirement for internal quality control and quality assurance. DAIDS staff or their designees will provide guidance on the development of an internal Quality Management Plan and will periodically require reporting on the outcome of these activities.

Internal Quality Management activities when integrated into the research project will allow planning for effective protocol implementation, assure compliance with sponsor requirements, identify areas in need of corrective action, verify the accuracy of data and assure a constant state of readiness for an external audit or monitoring visit.

An internal QM Plan is an evolving document that should be simple to follow and meet the needs of the research endeavor. *The guidance listed below are the minimum requirements for DAIDS funded clinical research sites.*

4.0 DEFINITIONS

Quality Control (QC) - is the *real time, on-going ("day-to-day")* observation and documentation of a site's work processes to ensure that accepted procedures are being followed. For example, reviewing demographic information for accuracy on each Case Report Form (CRFs) page prior to entry into the database.

Quality Assurance (QA) - is a *periodic*, systematic, objective and comprehensive examination of the total work effort to determine the level of compliance with accepted Good Clinical Practice (GCP) standards. For example, a monthly peer review of source documents compared to CRF pages to determine adherence to protocol requirements.

Quality Management - is the overall system that includes all activities involved in Quality Assurance and Quality Control including the assignment of roles and responsibilities, the reporting of results and the resolution of issues identified during the review.

The **"Scope" -** is the number or types of items to be reviewed as part of the quality management plan. For example, during the monthly QA audit each clinician will review 4 study visits (in which they did not participate) for eligibility, adherence to the study and completeness of AE reporting.

The **"Sample size" -** is the *quantitative* selection of items for review.

Key indicators - are selected performance areas that are vital to compliance with accepted GCP standards of performance. For example, all enrollments should be verified for eligibility and proper implementation of the informed consent process.

Root cause analysis - is the identification of the *most basic* reason a problem, inadequate performance, or obstacle to improvement exists.

Note: For additional definitions see DAIDS glossary.

5.0 RESPONSIBILITIES

Oversight of NIAID funded clinical research is a responsibility shared by DAIDS Project/Program Officers, Medical Officers, local Institutional Review Boards (IRBs) or Ethics Committees (ECs) and ultimately the Principal Investigators.

The overall responsibility for internal quality management activities resides with the Principal Investigator but may be delegated to other clinical staff.

DAIDS or its designated contractor can provide assistance in the development of a QM plan, and provide tools or aids to assist in the process.

6.0 POLICY

DAIDS requires that all sites participating in Clinical Research develop and implement a meaningful Internal Quality Management Plan that includes the following basic elements: Clearly designated responsibility

6.1.1 PI is ultimately responsible

6.1.2 PI may delegate responsibility for development, implementation and supervision of QM activities to another clinician such as a physician or nurse (designated clinician must be listed in plan)

6.2 Quality Management Activities

6.2.1 Plan should describe processes

6.2.2 Quality Control (QC) - During the conduct of ongoing day to day activities staff should be checking forms for completeness and logic. For example, are all headers completed correctly on case report forms (CRFs), are all required fields completed, are dates correct. QC should be a continuous activity that is typically done on 100% of CRFs prior to entry into the database. This activity should help identify any error trends in completion of CRFs.

6.2.3 Quality Assurance (QA)-QA is an internal audit of various components of the research process to assess adherence to the protocol, local and sponsor policies, and to determine the accuracy of research records. It is a periodic review of a defined number of research records, for a defined period of time. For example, staff may evaluate key components of source documentation and compare them to completed CRFs for agreement, and/or track consent forms through the entire informed consent process. *A minimum of 30% of all*

subject visits per month must be audited. Selection of records for audit should be based on the following:

6.2.3.1. High risk protocols

6.2.3.2. Higher accruing intervention protocols

6.2.3.3. Initial enrollments in new protocols

6.2.3.4. Protocol visits conducted by new or less experienced staff members

6.3 Key Indicators to be audited (may be specific per study visit)

6.3.1 An internal QA audit involves comparison of source documents to the CRFs and protocol to ensure agreement. These indicators should be audited in each participant record selected for internal QA review.

6.3.2 In all studies audits should review at a minimum:

6.3.2.1. Informed consent and subject education

6.3.2.2. Eligibility criteria

6.3.2.3. Scheduled laboratory tests and procedures

6.3.2.4. Missed visits/tests

6.3.2.5. Compliance with unit and sponsor SOPs including GCP

6.3.3 Additionally, for interventional studies that include a study product, audits should review:

6.3.3.1. Concomitant medications

6.3.3.2. Prohibited Medications

6.3.3.3. Study Product administration/dosing

6.3.3.4. Clinical endpoint identification

6.3.3.5. Adverse Event (AE) identification and reporting

6.3.4 Assessment of AEs for reporting to DAIDS, IRB/EC, and regulatory authorities.

6.4 The plan should describe what QM activities will be performed to ensure that the contents of regulatory files are complete and up to date.

6.5 The plan should describe what types of "tools" or check lists will be used in the QA and QC process. Examples include the following:

6.5.1 Visit reminder checklists

6.5.2 Audit worksheets which should contain the following:

6.5.2.1. Name of the reviewer

6.5.2.2. Date of the review

6.5.2.3. Patient Identification (PID) numbers of CRFs and source documents reviewed

6.5.2.4. Specific items that were reviewed

6.5.2.5. Time period covered by the review

6.5.2.6. Findings/results of review

6.5.3 Data entry, query or transmission reports from data management center (DMC) (where applicable)

6.5.4 Error reports from DMC (where applicable)

6.5.5 Clinical site monitoring reports

6.5.6 Summary reports from internal QA/QC findings

6.5.7 Other QA/QC aids used to review regulatory files, protocol deviations, or CRFs

6.6 The plan should include how the results of internal audits are summarized and how findings are analyzed and communicated. The following items should be included in annual reports but may be requested by DAIDS on a more frequent basis.

6.6.1 An identification of problem areas

6.6.2 Site staff participation in the reviews

6.6.3 Exploration of possible causes for problems (root cause analysis)

6.6.4 Corrective actions taken

6.6.5 Any revisions made to the QM plan to address problem areas identified

7.0 REFERENCES

None.

8.0 INQUIRIES

Questions and comments regarding this policy may be directed to the OPCRO Policy Group at:

NIAIDOPCROPOLICYGROUP@mail.nih.gov

9.0 AVAILABILITY

This policy is available electronically at the following URL:
http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Default.htm

The signed original is maintained in the OPCRO policy office.

10.0 CHANGE SUMMARY

Version #	Date	Replaces	Date of Revision	Rationale for Revision/Retirement
1.0	14 JUL 06	N/A	N/A	N/A

11.0 APPENDICES

None.

12.0 APPROVAL

	Signature	Program/Branch	Date
Authorized By:	Richard Hafner Richard Hafner, MD Director	Office for Policy in Clinical Research Operations	July 14, 2006